

ASYMPTOTICS OF STOCHASTIC PROTEIN ASSEMBLY MODELS

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ABSTRACT. Self-assembly of proteins is a biological phenomenon which gives rise to spontaneous formation of *amyloid fibrils* or *polymers*. The starting point of this phase, called *nucleation* exhibits an important variability among replicated experiments. To analyse the stochastic nature of this phenomenon, one of the simplest models considers two populations of chemical components: monomers and polymerised monomers. Initially there are only monomers. There are two reactions for the polymerization of a monomer: either two monomers collide to combine into two polymerised monomers or a monomer is polymerised after the encounter of a polymerised monomer. It turns out that this simple model does not explain completely the variability observed in the experiments. This paper investigates extensions of this model to take into account other mechanisms of the polymerization process that may have impact on fluctuations. The first variant consists in introducing a preliminary conformation step to take into account the biological fact that, before being polymerised, a monomer has two states, regular or misfolded. Only misfolded monomers can be polymerised so that the fluctuations of the number of misfolded monomers can be also a source of variability of the number of polymerised monomers. The second variant, based on numerical considerations, represents the reaction rate α of spontaneous formation of a polymer as of the order of $N^{-\nu}$, for some large scaling variable N representing the reaction volume and ν some positive constant. Asymptotic results involving different time scales are obtained for the corresponding Markov processes. First and second order results for the starting instant of nucleation are derived from these limit theorems. The proofs of the results rely on a study of a stochastic averaging principle for a model related to an Ehrenfest urn model, and also on a scaling analysis of a population model.

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1. INTRODUCTION

Self-assembly of proteins is an important biological phenomenon, on the one hand associated with human diseases such as Alzheimer's, Parkinson's, Huntington's diseases and still many others, and on the other hand involved in industrial processes, see McManus et al. [20] and Ow and Dustan [22]. The initial step of the chain reactions giving rise to amyloid fibrils consists in the spontaneous formation of a so-called *nucleus*, that is, the simplest possible polymer able to ignite the

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reaction. This early phase is called *nucleation*, and is still far from being understood. As underlined by previous studies Szavits-Nossan et al. [28], the nucleation step is intrinsically stochastic, leading to an important variability among replicated experiments, not only in small volumes but even in relatively large ones, see Xue et al. [29]. The question of building convenient stochastic models, able to render out the heterogeneity observed, and even to predict it, has recently raised much interest in the biological and biophysical community, see Szavits-Nossan et al. [28], Yvinec et al. [30], Pigolotti et al. [24] and Eden et al. [9].

We start with a simple stochastic model, proposed and studied in Eugène et al. [10] for which we consider extensions to get a deeper understanding on the intricate influence of each reaction considered. In Eugène et al. [10], rigorous asymptotics of the simple model were proved, and it was fitted to the experimental data published in Xue et al [29]. It was shown that the predicted variability was much smaller by the model than what was experimentally obtained. One of the conclusions of this work is that other mechanisms had to be taken into account to explain the variability observed in the experiments. We thus propose here two ways to complement the basic model. Let us first recall its definition.

1.1. The Basic Model. One of the simplest models to describe the nucleation process considers two populations of chemical components: (regular) monomers and polymerised monomers. Initially there are only monomers. There are two reactions for the polymerization of a monomer: either two monomers collide to combine into two polymerised monomers or a monomer is polymerised after the encounter of a polymerised monomer. The chemical reactions associated with the basic model can then be described as follows:



These reactions can be represented by the sample paths of a Markov process $(X_1^N(t), X_2^N(t))$, where $X_1^N(t)$ [resp. $X_2^N(t)$] is the number of regular [resp. polymerised] monomers at time $t \geq 0$. The scaling variable N which will be used should be thought of as the reaction volume. In particular $X_2^N(t)/N$ is the concentration of polymerised monomers at time t . If M_N is the initial number of monomers, it is assumed that the following regime

$$(2) \quad \lim_{N \rightarrow +\infty} \frac{M_N}{N} = m$$

holds for some $m > 0$. The quantity M_N/N is in fact the initial concentration of monomers.

The transition rates of $(X_1^N(t), X_2^N(t))$ are given by, for $x = (x_1, x_2) \in \mathbb{N}^2$,

$$(3) \quad x \mapsto \begin{cases} x + (-2, 2) & \text{at rate } \alpha(x_1/N)^2 \\ x + (-1, 1) & \beta x_1/N \times x_2/N. \end{cases}$$

The second coordinate x_2 is in fact the polymerized mass which explains the jumps of size 2 in the reactions. Note that the conservation of mass implies that the quantity $X_1^N(t) + X_2^N(t)$ is constant and equal to M_N , the total number of initial monomers.

- The first reaction of (1) converts two monomers into two polymerised monomers. In our model, due to thermal noise in particular, these reactions will occur in a stochastic way. Following the principles of the law of mass action, the encounter of two chemical species occurs at a rate proportional to the product of the *concentrations* of each species. Therefore two given monomers disappear to produce two polymerised monomers at a rate $\alpha(x_1/N)^2$.
- The second reaction can be seen as an auto-catalytic process. Here, given a monomer at the contact of a polymerised monomer, the monomer is converted into a polymerised monomer at a rate β . Again, by the law of mass action, regular monomers disappear at the rate $\beta(x_1/N)(x_2/N)$.

See Eugène et al. [10], Szavits-Nossan et al. [28] and Xue et al. [29] for a general presentation of these phenomena in a biological context. For more discussion and results on stochastic models associated to chemical reactions, see for example Anderson and Kurtz [1] and Higham [13] and references therein.

This simple, intuitive model of polymerisation has the advantage of having only two parameters to determine. It can be analyzed mathematically by standard tools of probability theory, see Eugène et al. [10]. It has been shown that if $X_2^N(t)$ is the number of polymerised monomers at time t , then the polymerisation process can be described via the following convergence in distribution

$$(4) \quad \lim_{N \rightarrow +\infty} \left(\frac{X_2^N(Nt)}{N} \right) = (x_2(t))$$

holds, where $(x_2(t))$ is the non-trivial solution of the following simple ordinary differential equation

$$(5) \quad \dot{x}_2(t) = \alpha(m - x_2(t))^2 + \beta(m - x_2(t))x_2(t)$$

converging to m as t goes to infinity.

By using these simple mathematical results and the data from experiments with 17 different concentrations of monomers (the value of m) and 12 experiments for each concentration, Table I of Eugène et al. [10] shows that, in this setting, the estimation of β is reasonably robust. This is unfortunately not the case for the numerical estimation of α which is varying from $1.68 \cdot 10^{-2}$ to $9.57 \cdot 10^{-8}$. An additional difficulty with this simple model comes from the small values of α obtained. Indeed, for the experiments, the value of the volume N is in the order of 10^{15} , some of the estimated values of α in 10^{-8} are therefore, numerically, of the order of $1/\sqrt{N}$. The asymptotic results are obtained when N gets large and α *fixed*. For this reason, one may suspect a problem of convergence speed in Relation (4) when these parameters are used. It turns out that our simulations confirm that the asymptotic regime (4) does not seem to represent accurately the system when α is too small.

The purpose of the present paper is to refine this basic model in two different ways.

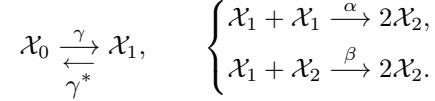
- (1) The model can be improved by introducing a key feature of the polymerisation process: the misfolding of monomers. Experiments show that monomers can be polymerised only if their 3-D structure has been modified by some events. Such monomers are called misfolded monomers, see Dobson [7, 8], Knowles et al. [17]. It turns out that, at a given time, only

a small fraction of monomers are misfolded which may also explain that the polymerisation process starts very slowly. In biological cells, this phenomenon of misfolding is reversible, dedicated proteins may “correct” the misfolded monomers. A misfolded monomer can be turned into a “regular” monomer and vice-versa. See Bozaykut et al. [4] and Lanneau et al. [19] for example. Section 3 is devoted to the mathematical analysis of these models.

- (2) Another approach is to keep the basic model but with the parameter α being of the order of $1/N^\nu$ for some positive ν to take into account that, in practice, the values of this parameter can be very small. Note that this is only a numerical observation, the value of α has no reason to depend on the volume. This model is analyzed in Section 3.

The rest of the section is devoted to a brief sketch of the mathematical aspects of these two classes of models. As it will be seen, the models are more challenging from a mathematical point of view, the model with misfolded monomers in particular.

1.2. Models with Misfolding Phenomena. The chemical reactions associated with this simple model are as follows:



At time $t \geq 0$, $X_0^N(t)$ denotes the number of regular monomers, $X_1^N(t)$ the number of misfolded monomers. As before the last coordinate $X_2^N(t)$ is the polymerized mass. As a Markov process, $(X^N(t)) = (X_0^N(t), X_1^N(t), X_2^N(t))$ has the following transitions, for an element $x = (x_0, x_1, x_2) \in \mathbb{N}^3$,

$$(6) \quad x \mapsto \begin{cases} x+(1, -1, 0) & \text{at rate } \gamma^* x_1 \\ x+(-1, 1, 0) & \gamma x_0, \end{cases} \quad x \mapsto \begin{cases} x+(0, -2, 2) & \alpha (x_1/N)^2 \\ x+(0, -1, 1) & \beta x_1/N \times x_2/N. \end{cases}$$

It is important to note that the transition between state “0”, regular monomer, and state “1”, misfolded monomer, is spontaneous. Consequently, as it can be seen, the corresponding transition rates *do not* depend on the volume N but simply on the numbers of components and not on their concentrations. An important consequence of this observation is that the system exhibits a two time scales behavior that we will investigate.

An informal description of the asymptotic behavior of $(X_2^N(t))$. The first two coordinates can be seen as an Ehrenfest process with two urns 0 and 1 where each particle in urn 0 (resp. 1) goes to urn 1 (resp. 0) at rate γ (resp. γ^*). See Bingham [3] and Karlin and McGregor [16] for example. Particles in urn 1 can also go to the urn 2 corresponding to the polymerized mass but this phenomenon occurs at a much slower rate so that, locally, it does not change the orders of magnitude in N of X_2^N .

When $X_2^N \sim x_2 N$, there is a total of $(m-x_2)N$ particles in the urns 0 or 1. The components $(X_0^N(t), X_1^N(t))$ are both of the order of N and are moving on a fast time scale, proportional to N . The transition rates of the process $(X_2^N(t))$ are slower, bounded with respect to N . Because of the fast transition rates of the first two coordinates, the Ehrenfest urn process should reach quickly an equilibrium

for which X_0^N has a binomial distribution with parameter $(m - x_2)N$ and r with $r = \gamma/(\gamma + \gamma^*)$, in particular

$$\frac{X_0^N}{N} \sim (1 - r)(m - x_2) \text{ and } \frac{X_1^N}{N} \sim r(m - x_2).$$

This suggests that,

- a) to see an evolution of X_2^N of the order of N , one has to be on the linear time scale $t \mapsto Nt$: transition rates of the process X_2^N are $O(1)$,
- b) if $X_2^N(Nt) \sim x_2(t)N$, in view of transition rates of $(X_2^N(t))$ of Relation (6), then $(x_2(t))$ should satisfy the following ordinary differential equation

$$(7) \quad \dot{x}_2(t) = \alpha r^2(m - x_2(t))^2 + \beta r(m - x_2(t))x_2(t).$$

We recognize the limit equation (5) of the simple model, where α, β are respectively replaced by αr^2 and βr . This result is also true when considering the second order fluctuations of the number of polymers, see Theorem 2. The proof of the convergence of the process of the concentration of polymerized monomers to the solution of the ODE (5) use standard arguments of convergence of a sequence of stochastic processes, see the supplementary material of Eugène et al. [10]. The proof of the corresponding result with misfolding phenomena for the ODE (7) is, as we shall see, more delicate to handle.

Stochastic Averaging Phenomenon. To summarize these observations, the coordinates $(X_0^N(t), X_1^N(t))$ form a “fast” process and $(X_2^N(t))$ is a “slow” process when the scaling parameter N goes to infinity. This suggests a stochastic averaging principle (SAP) in a fully coupled context.

- (1) The stochastic evolution of $(X_2^N(Nt))$ is driven by the invariant distribution of an “instantaneous” associated Ehrenfest process.
- (2) The parameters of the Ehrenfest process depend on the macroscopic variable $(X_2^N(Nt))$.

see Papanicolaou et al. [23] and Chapter 8 of Freidlin and Wentzell [11] for example, see also Kurtz [18].

A stochastic averaging principle is indeed proved as well as a corresponding central limit theorem (CLT). In our cases there are some differences with the “classical” framework of stochastic averaging principles. The state space of the fast process depends on the scaling parameter N , and is not in particular a “fixed” process (with varying parameters) as it is usually the case. See Hunt and Kurtz [14] or Sun et al. [27] for example. A law of large numbers with respect to N for the invariant distribution of the fast process is driving the evolution of the slow process. The approach used in the paper relies on the use of occupation measures on a continuous state space instead of a discrete space, this leads to some technical complications as it will be seen. Concerning central limit theorems in a SAP context, there are few references available for jump processes. The methods presented in Kang et al. [15] or in Sun et al. [27] do not seem to be helpful in our case. Instead, an ad-hoc estimation, Proposition 4, gives the main ingredient to derive a central limit theorem, see Section 2.

1.3. Models with Scaled Reaction Rates. Again, $X_1^N(t)$ (resp. $X_2^N(t)$) is the number of regular (resp. polymerised) monomers at time $t \geq 0$. The transition rates of the Markov process $(X^N(t)) = (X_1^N(t), X_2^N(t))$ associated to these models

are the same, except that the parameter α is replaced by α/N^ν with $0 < \nu$. For $x = (x_1, x_2) \in \mathbb{N}^2$, the rates are given by

$$(8) \quad x \mapsto \begin{cases} x+(-2, 2) & \text{at rate } \alpha/N^\nu (x_1/N)^2 \\ x+(-1, 1) & \beta x_1/N \times x_2/N. \end{cases}$$

Convergence (4) shows that the polymerisation occurs on the linear time scale $t \mapsto Nt$ for the basic model. It will be shown that the phenomenon does not start on this time scale. A slightly more rapid time scale is necessary for this purpose, it is shown that it is on the time scale $t \mapsto N \log N \cdot t$ for $0 < \nu \leq 1$ and $t \mapsto N^\nu t$ when $\nu > 1$. See Section 3.

2. STOCHASTIC MODELS WITH MISFOLDING PHENOMENA

The following notations will be used throughout the paper. For $\xi \geq 0$, $\mathcal{N}_\xi(dt)$ denotes a Poisson process with parameter ξ and $(\mathcal{N}_\xi^i(dt))$ an i.i.d. sequence of such processes. All the Poisson processes are defined on a probability space $(\Omega, \mathcal{F}, \mathbb{P})$. If f is a real valued function on \mathbb{R}_+ , $f(t-)$ denotes its limit on the left of $t \geq 0$ when it exists. Finally, m^* denotes an upper bound for the sequence (M_N/N) which converges to $m > 0$ by Relation (2).

Recall that, at time $t \geq 0$, $(X^N(t)) = (X_0^N(t), X_1^N(t), X_2^N(t))$ where $X_0^N(t)$ is the number of monomers, $X_1^N(t)$ is the number of misfolded monomers and $X_2^N(t)$ is the polymerized mass. It is not difficult to see that these processes can be seen as the solution of the following stochastic differential equations,

$$(9) \quad \begin{cases} dX_0^N(t) = \sum_{i=1}^{X_1^N(t-)} \mathcal{N}_{\gamma^*}^i(dt) - \sum_{i=1}^{X_0^N(t-)} \mathcal{N}_\gamma^i(dt), \\ dX_2^N(t) = 2 \sum_{i=1}^{X_1^N(t-)(X_1^N(t-)-1)/2} \mathcal{N}_{\alpha/N^2}^i(dt) + \sum_{i=1}^{X_1^N(t-)X_2^N(t-)} \mathcal{N}_{\beta/N^2}^i(dt), \end{cases}$$

with the relation of conservation of mass $M_N = X_0^N(t) + X_1^N(t) + X_2^N(t)$ and initial condition $X^N(0) = (M_N, 0, 0)$.

Equation (9) gives in particular that

$$(10) \quad X_2^N(t) = X_2^N(0) + \frac{\alpha}{N^2} \int_0^t X_1^N(s)(X_1^N(s)-1) ds + \frac{\beta}{N^2} \int_0^t X_1^N(s)X_2^N(s) ds + M_2^N(t),$$

where $(M_2^N(t))$ is a martingale whose previsible increasing process is given by

$$(11) \quad \langle M_2^N \rangle(t) = 2 \frac{\alpha}{N^2} \int_0^t X_1^N(s)(X_1^N(s)-1) ds + \frac{\beta}{N^2} \int_0^t X_1^N(s)X_2^N(s) ds$$

For $i = 0, 1, 2$ and $t \geq 0$, denote

$$\bar{X}_i^N(t) = \frac{X_i^N(Nt)}{N},$$

the main goal of this section is to prove that the process $(\bar{X}_2^N(t))$ is converging in distribution to the solution $(x_2(t))$ of a non-trivial ordinary differential equation. It will show in particular that the polymerization process is occurring on the linear time scale $t \mapsto Nt$.

2.1. Random Measures Associated to Occupation Times. Define μ_N the random measure on \mathbb{R}_+^3 by

$$\langle \mu_N, g \rangle = \int_{\mathbb{R}_+} g(\bar{X}_0^N(Nu), \bar{X}_1^N(Nu), u) \, du.$$

Proposition 1. *The sequence (μ_N) is tight. Any limiting point μ_∞ of this sequence is such that*

$$(12) \quad \langle \mu_\infty, g \rangle = \int_{\mathbb{R}_+^3} g(x, y, u) \, \pi_u(dx, dy) \, du,$$

for any continuous function g on $[0, m^*]^2 \times [0, T]$, where for each $u \geq 0$, π_u is a random Radon measure on \mathbb{R}_+^2 .

Proof. Since $\bar{X}_0^N(t)$ and $\bar{X}_1^N(t)$ are bounded, for any $T > 0$, the measure μ_N restricted to the set $\mathbb{R}_+^2 \times [0, T]$ has a compact support. Lemma 3.2.8 page 44 of Dawson [5] gives directly that the sequence (μ_N) of random measure on \mathbb{R}_+^3 is tight.

Let (μ_{N_k}) be a convergent subsequence with limit μ_∞ . By using Skorohod's representation theorem, one can assume that there exists a negligible measurable set \mathcal{A} of the probability space such that, outside this subset, the convergence of the sequence (μ_{N_k}) of Radon measures towards μ_∞ , that is

$$\lim_{k \rightarrow +\infty} \langle \mu_{N_k}, g \rangle = \langle \mu_\infty, g \rangle \text{ for all } g \in C([0, m^*]^2 \times [0, T]),$$

holds.

Let $h \in C([0, m^*]^2)$ and $f \in C([0, T])$, denoting $h \otimes f(x, y, u) = h(x, y)f(u)$, for $(x, y) \in [0, m^*]^2$ and $u \in [0, T]$, then, as a limit of the sequence (μ_{N_k}) , the Radon measure

$$f \mapsto \langle \mu_N, h \otimes f \rangle$$

is absolutely continuous with respect to Lebesgue's measure. Consequently, for any $h \in C([0, m^*]^2)$, there exists some function $(\tilde{\pi}_u(h), 0 \leq u \leq T)$ such that

$$\langle \mu_\infty, h \otimes f \rangle = \int_0^T \tilde{\pi}_u(h) f(u) \, du.$$

By the differentiation theorem, see Theorem 7.10 in Rudin [26], the function $(\tilde{\pi}_u(h))$ can be represented as

$$\tilde{\pi}_u(h) = \limsup_{\varepsilon \rightarrow 0} \frac{1}{\varepsilon} \langle \mu_\infty, h \otimes \mathbb{1}_{[u-\varepsilon/2, u+\varepsilon/2]} \rangle, \quad u \in [0, T],$$

consequently, the mapping $(\omega, u) \mapsto \tilde{\pi}_u(h)(\omega)$ is $\mathcal{F} \otimes \mathcal{B}([0, T])$ -measurable.

Let \mathcal{S} be a countable dense subset of $C([0, m^*]^2)$, then there exists a subset E_0 of $[0, T]$ negligible for the Lebesgue measure such that, for all $u \in [0, T] \setminus E_0$ and $\phi_1, \phi_2 \in \mathcal{S}$,

- (1) $\tilde{\pi}_u(p_1\phi_1 + p_2\phi_2) = p_1\tilde{\pi}_u(\phi_1) + p_2\tilde{\pi}_u(\phi_2)$, $\forall p_1, p_2 \in \mathbb{Q}$,
- (2) $\tilde{\pi}_u(\phi_1) \leq \tilde{\pi}_u(\phi_2)$ if $\phi_1 \leq \phi_2$,
- (3) $\tilde{\pi}_u(1) = 1$.

With the same method as in Section II.88 of Rogers and Williams [25], for any $u \in [0, T] \setminus E_0$, one gets the existence of a Radon measure π_u on $[0, m^*]^2$ such that

$\tilde{\pi}_u(h) = \pi_u(h)$ for any $h \in \mathcal{S}$. By density of \mathcal{S} , the mapping $(\omega, u) \mapsto \pi_u(h)(\omega)$ is also $\mathcal{F} \otimes \mathcal{B}([0, T])$ -measurable and the relation

$$\langle \mu_\infty, h \otimes f \rangle = \int_0^T \pi_u(h) f(u) \, du.$$

holds for all $h \in C([0, m^*]^2)$ and $f \in C([0, T])$. The proposition is therefore proved. \square

Representation (12) is related to Lemma 1.4 of Kurtz [18]. Our proof relies on classical arguments of measure theory, a functional version of Carathéodory's extension theorem in particular which is described in Section II.88 of Rogers and Williams [25]. In Kurtz [18], a more sophisticated result, see Morando [21], on the extension of bi-measures is the key ingredient. The notion of bi-measure goes back to Kingman, see Dellacherie and Meyer [6] for example. It should be mentioned that Lemma 1.4 of Kurtz [18] gives also additional measurability properties of the family (π_u) which are of no use in our case.

Proposition 2. *If μ_∞ is a limiting point of (μ_N) with the representation (12) then, for any \mathcal{C}^1 -function f on \mathbb{R}_+^2 , almost surely*

$$(13) \quad \int_0^t \int_{\mathbb{R}_+^2} (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} f(x, y) - \frac{\partial}{\partial y} f(x, y) \right) \pi_u(dx, dy) \, du = 0, \quad \forall t \geq 0,$$

in particular, almost surely,

$$(14) \quad \int_0^t \int_{\mathbb{R}_+^2} (\gamma^* y - \gamma x)^2 \pi_u(dx, dy) \, du = 0, \quad \forall t \geq 0.$$

Relation (14) just says that almost surely and for almost all u , the measure π_u is degenerated on \mathbb{R}_+^2 and carried by the subset $\{(x, \gamma x / \gamma^*) : 0 \leq x \leq m\}$.

Proof. for $(i, j) \in \mathbb{Z}^2$, one denotes by Δ_{ij} the discrete differential operator

$$\Delta_{ij}^N(f)(x, y) = f(x + i/N, y + j/N) - f(x, y), \quad (x, y) \in [0, m^*]^2.$$

After some trite calculations, the stochastic differential equations (9) give the relation

$$(15) \quad \begin{aligned} f\left(\bar{X}^N(t/N)\right) &= f\left(\bar{X}^N(0)\right) + \gamma \int_0^t X_0^N(s) \Delta_{-1,1}^N(f)\left(\bar{X}^N(s/N)\right) \, ds \\ &\quad + \gamma^* \int_0^t X_1^N(s) \Delta_{1,-1}^N(f)\left(\bar{X}^N(s/N)\right) \, ds \\ &\quad + \alpha \int_0^t \frac{X_1^N(s)(X_1^N(s) - 1)}{2N^2} \Delta_{0,-2}^N(f)\left(\bar{X}^N(s/N)\right) \, ds \\ &\quad + \beta \int_0^t \frac{X_1^N(s)}{N} \frac{X_2^N(s)}{N} \Delta_{0,-1}^N(f)\left(\bar{X}^N(s/N)\right) \, ds + M_f^N(t), \end{aligned}$$

where $(\bar{X}^N(t)) = (X_0^N(Nt)/N, X_1^N(Nt)/N)$ and $(M_f^N(t))$ is the associated martingale. Its previsible increasing process is given by

$$(16) \quad \begin{aligned} \langle M_f^N \rangle(t) = & \gamma \int_0^t X_0^N(s) \Delta_{-1,1}^N(f)^2 \left(\bar{X}^N(s/N) \right) ds \\ & + \gamma^* \int_0^t X_1(s) \Delta_{1,-1}^N(f)^2 \left(\bar{X}^N(s/N) \right) ds \\ & + \alpha \int_0^t \frac{X_1^N(s)(X_1^N(s) - 1)}{2N^2} \Delta_{0,-2}^N(f)^2 \left(\bar{X}^N(s/N) \right) ds \\ & + \beta \int_0^t \frac{X_1^N(s)}{N} \frac{X_2^N(s)}{N} \Delta_{0,-1}^N(f)^2 \left(\bar{X}^N(s/N) \right) ds. \end{aligned}$$

Note that, for $i, j \in \mathbb{Z}$

$$\Delta_{i,j}^N(f)(x, y) = \frac{1}{N} \left(i \frac{\partial f}{\partial x}(x, y) + j \frac{\partial f}{\partial y}(x, y) \right) + o(1/N),$$

by changing the time variable in Nt in Equation (15) and by dividing by N one gets the relation

$$(17) \quad \begin{aligned} \frac{1}{N} \left(f \left(\bar{X}^N(t) \right) - f \left(\bar{X}^N(0) \right) \right) \\ = \int_0^t \left[\gamma^* \bar{X}_1^N(s) - \gamma \bar{X}_0^N(s) \right] \left[\frac{\partial f}{\partial x} - \frac{\partial f}{\partial y} \right] \left(\bar{X}^N(s) \right) ds \\ - \frac{\alpha}{N} \int_0^t \bar{X}_1^N(s) \left(\bar{X}_1^N(s) - 1/N \right) \frac{\partial f}{\partial y} \left(\bar{X}^N(s) \right) ds \\ - \frac{\beta}{N} \int_0^t \bar{X}_1^N(s) \bar{X}_2^N(s) \frac{\partial f}{\partial y} \left(\bar{X}^N(s) \right) ds + \frac{M_f^N(Nt)}{N} + o(1/N), \end{aligned}$$

with $(\bar{X}^N(t)) = (\bar{X}_0^N(t), \bar{X}_1^N(t))$. The previsible increasing process of the martingale $(M_f^N(Nt)/N)$ in the above expression is $(\langle M_f^N \rangle(Nt)/N^2)$. By using Equation (16) and the fact that $(\bar{X}_i^N(t))$ is bounded for $i = 0$ and 1 , it is not difficult to show that its expected value converges to 0 as N gets large and, by Doob's Inequality, that the martingale converges in distribution to 0. With similar arguments, from Equation (17), one gets therefore the following convergence in distribution

$$(18) \quad \lim_{N \rightarrow +\infty} \left(\int_0^t \left[\gamma^* \bar{X}_1^N(s) - \gamma \bar{X}_0^N(s) \right] \left[\frac{\partial f}{\partial x} - \frac{\partial f}{\partial y} \right] \left(\bar{X}^N(s) \right) ds \right) = 0.$$

For $t \geq 0$,

$$\begin{aligned} \int_0^t \left[\gamma^* \bar{X}_1^N(s) - \gamma \bar{X}_0^N(s) \right] \left[\frac{\partial f}{\partial x} - \frac{\partial f}{\partial y} \right] \left(\bar{X}^N(s) \right) ds \\ = \int [\gamma^* y - \gamma x] \left[\frac{\partial f}{\partial x} - \frac{\partial f}{\partial y} \right] (x, y) \mathbb{1}_{\{s \leq t\}} \mu_N(dx, dy, ds), \end{aligned}$$

and this last term converges in distribution to

$$\begin{aligned} & \int [\gamma^* y - \gamma x] \left[\frac{\partial f}{\partial x} - \frac{\partial f}{\partial y} \right] (x, y) \mathbb{1}_{\{u \leq t\}} \mu_\infty(dx, dy, du) \\ &= \int_0^t \int_{\mathbb{R}_+^2} (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} f(x, y) - \frac{\partial}{\partial y} f(x, y) \right) \pi_s(dx, dy) ds. \end{aligned}$$

This convergence in distribution also holds for any finite marginals of this process. The convergence of processes (18) gives therefore the desired identity (13) in distribution. The last assertion of the proposition is proved by taking the function $f(x, y) = \gamma^* y^2 - \gamma x^2$. \square

2.2. A Stochastic Averaging Principle. Relation (10) gives the following integral equation for $(\bar{X}_2^N(t))$,

$$\begin{aligned} (19) \quad \bar{X}_2^N(t) &= \bar{X}_2^N(0) + \alpha \int_0^t \bar{X}_1^N(s) (\bar{X}_1^N(s) - 1/N) ds \\ &\quad + \beta \int_0^t \bar{X}_1^N(s) \bar{X}_2^N(s) ds + \frac{M_2^N(Nt)}{N}, \end{aligned}$$

The expected value of the previsible increasing process of the martingale converges $M_2^N(Nt)/N$ is vanishing as N gets large by Equation (11). Doob's Inequality shows that the martingale converges in distribution to 0. The criteria of the modulus of continuity, see Billingsley [2], gives therefore that the sequence of processes $(\bar{X}_2^N(t))$ is tight. It can therefore be assumed, for some subsequence (N_k) , that the following convergence holds,

$$\lim_{k \rightarrow +\infty} \left(\mu_{N_k}, \left(\bar{X}_2^{N_k}(t) \right) \right) = (\mu_\infty, (x_2(t)))$$

for a random measure μ_∞ as in Proposition 1 and some continuous stochastic process $(x_2(t))$. The rest of the section is devoted to the identification of $(x_2(t))$.

Proposition 3. *For any continuous function g on $[0, m]^2$, the relation*

$$\left(\int_0^t g(x, y) \mu_\infty(dx, dy) du \right) \stackrel{dist.}{=} \left(\int_0^t g((m - x_2(u))(1 - r, r)) du \right)$$

holds, with $r = \gamma/(\gamma + \gamma^)$.*

One concludes that the measure $\pi_u(dx, dy)$ of Proposition 1 is simply the Dirac measure at $[m - x_2(u)](1 - r, r)$. This is the rigorous description of the fact described at the beginning of this section that if the fraction of polymerized mass is $x_2(u)$ then the fraction of regular [resp. misfolded] monomers is $(1 - r)(m - x_2(u))$ [resp. $r(m - x_2(u))$].

Proof. The criteria of the modulus of continuity shows that the sequence of processes

$$\left(\int_0^t g(\bar{X}_0^{N_k}(u), \bar{X}_1^{N_k}(u)) du \right)$$

is tight. By convergence in distribution of (μ_{N_k}) , one has, for $t \geq 0$,

$$(20) \quad \lim_{k \rightarrow +\infty} \int_0^t g\left(\bar{X}_0^{N_k}(u), \bar{X}_1^{N_k}(u)\right) du \\ \int_0^t g(x, y) \pi_u(dx, dy) du = \int_0^t g\left(x, \frac{\gamma}{\gamma^*} x\right) \pi_u(dx, dy) du$$

by Proposition 2. The same convergence in distribution also holds for finite marginals. One has to identify the first marginal of (π_u) . If f is a continuous function on $[0, m^*]$, by conservation of mass, one has the relation

$$\left(\int_0^t f\left(\bar{X}_0^{N_k}(u) + \bar{X}_1^{N_k}(u)\right) du\right) = \left(\int_0^t f\left(\frac{M_{N_k}}{N_k} - \bar{X}_2^{N_k}(u)\right) du\right).$$

Relation (20) and the convergence properties of the right hand side of this identity give the following identity of processes

$$\left(\int_0^t f(x/r) \pi_u(dx, dy) du\right) = \left(\int_0^t f(m - x_2(u)) du\right).$$

The proposition is proved. \square

Theorem 1. *Under the scaling condition (2) and if the initial state of the solution $(X^N(t))$ of the SDE (9) is $X^N(0) = (M_N, 0, 0)$ then, for the convergence in distribution,*

$$(21) \quad \lim_{N \rightarrow +\infty} \left(\frac{X_2^N(Nt)}{N}\right) = (x_2(t)) \stackrel{\text{def.}}{=} \left(\frac{1 - e^{-\beta r m t}}{1 + (\beta/\alpha r - 1)e^{-\beta r m t}} m\right),$$

with $r = \gamma/(\gamma + \gamma^*)$.

Proof. By using Relation (19), Proposition 1 and the above proposition, one gets that any limiting point $(x_2(t))$ of $(X_2^N(Nt)/N)$ satisfies necessarily the following integral equation (integral form of the equation (7))

$$(22) \quad x_2(t) = \alpha r^2 \int_0^t (m - x_2(s))^2 ds + \beta r \int_0^t (m - x_2(s)) x_2(s) ds.$$

By uniqueness of the solution of this equation, one gets the convergence in distribution of the sequence of processes $(X_2^N(Nt)/N)$. Its explicit expression is easily obtained. \square

The following corollary gives the asymptotics of the first instant when a fraction $\delta \in (0, 1)$ of monomers has been polymerized. This is a key quantity that can be measured with experiments.

Corollary 1. *[Asymptotics of Lag Time] Under the conditions of Theorem 1, if for $\delta \in (0, 1)$,*

$$(23) \quad T^N(\delta) = \inf\{t \geq 0 : X_2^N(t)/M_N \geq \delta\},$$

then, for the convergence in distribution

$$(24) \quad \lim_{N \rightarrow +\infty} \frac{T^N(\delta)}{N} = t_\delta \stackrel{\text{def.}}{=} \frac{1}{r m \beta} \log \left(1 + \frac{\delta \beta}{\alpha r (1 - \delta)}\right).$$

2.3. Central Limit Theorem. From Proposition 2, it has been proved that if $f : [0, m^*]^2$ is a \mathcal{C}^1 -function then, for the convergence in distribution

$$\lim_{N \rightarrow +\infty} \left(\int_0^t (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} f(x, y) - \frac{\partial}{\partial y} f(x, y) \right) \mu_N(dx, dy, ds) \right) = (0),$$

with the above notations, The following proposition is an extension of this result. This is the key ingredient to prove the central limit result of this section.

Proposition 4. *If $g : [0, m^*]^2 \times \mathbb{R}_+$ is a \mathcal{C}^1 -function then, for the convergence in distribution,*

$$\lim_{N \rightarrow +\infty} \left(\int_0^t (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} g(x, y, u) - \frac{\partial}{\partial y} g(x, y, u) \right) \sqrt{N} \mu_N(dx, dy, du) \right) = (0).$$

Proof. We follow the same lines as in the proof of Proposition 2. The analogue of Relation (17) is

$$\begin{aligned} (25) \quad & \frac{1}{\sqrt{N}} \left(g(\bar{X}^N(t), t) - g(\bar{X}^N(0), 0) \right) \\ &= \sqrt{N} \int_0^t (\gamma^* y - \gamma x) \left(\frac{\partial}{\partial x} g(x, y, s) - \frac{\partial}{\partial y} g(x, y, s) \right) \mu_N(dx, dy, ds) \\ &\quad - \frac{\alpha}{\sqrt{N}} \int_0^t \bar{X}_1^N(s) \left(\bar{X}_1^N(s) - 1/N \right) \frac{\partial f}{\partial y}(\bar{X}^N(s)) ds \\ &\quad - \frac{\beta}{\sqrt{N}} \int_0^t \bar{X}_1^N(s) \bar{X}_2^N(s) \frac{\partial f}{\partial y}(\bar{X}^N(s)) ds \\ &\quad + \frac{1}{\sqrt{N}} \int_0^t \frac{\partial f}{\partial z}(\bar{X}^N(s), s) ds + \frac{M_g^N(Nt)}{\sqrt{N}} + o(1/\sqrt{N}), \end{aligned}$$

It is not difficult to check with the analogue of Relation (16) for the previsible increasing process of the martingale $(M_g^N(Nt)/\sqrt{N})$ that, for $t \geq 0$,

$$\lim_{N \rightarrow +\infty} \mathbb{E} \left(\left\langle \frac{M_g^N(Nt)}{\sqrt{N}} \right\rangle \right) = \lim_{N \rightarrow +\infty} \frac{\mathbb{E}(\langle M_g^N \rangle(Nt))}{N} = 0.$$

Consequently, by Doob's Inequality, the martingale of Relation (25) vanishes when N gets large. The desired convergence of the proposition is then easily derived. \square

Theorem 2 (Central Limit Theorem). *Under Condition (2) and if $(x_2(t))$ is the function defined by Relation (21) then, for the convergence in distribution,*

$$\lim_{N \rightarrow +\infty} \left(\frac{X_2^N(Nt) - Nx_2(t)}{\sqrt{N}} \right) = (U(t)),$$

where $(U(t))$ is the solution of the stochastic differential equation

$$(26) \quad dU(t) = \sqrt{\sigma(t)} dB(t) + h(t)U(t) dt,$$

and $(B(t))$ is a standard Brownian motion and

$$\begin{cases} \sigma(t) = 2\alpha r^2(m - x_2(t))^2 + \beta r(m - x_2(t))x_2(t) \\ h(t) = r(\beta - 2\alpha r)(m - x_2(t)) - \beta r x_2(t). \end{cases}$$

The corresponding result of Eugène et al. [10] when there is no misfolding phenomenon shows that the functions σ and h are similar if α and β are respectively replaced by αr^2 and βr .

Proof. Denote

$$U^N(t) = \frac{X_2^N(Nt) - Nx_2(t)}{\sqrt{N}} = \sqrt{N} \left(\bar{X}_2^N(t) - x_2(t) \right).$$

By combining Equation (19),

$$\bar{X}_2^N(t) = \alpha \int_0^t \bar{X}_1^N(s)^2 ds + \beta \int_0^t \bar{X}_1^N(s) \bar{X}_2^N(s) ds + \frac{M_2^N(Nt)}{N} + O(1/N)$$

and Relation (22),

$$(27) \quad x_2(t) = \alpha r^2 \int_0^t (m - x_2(s))^2 ds + \beta r \int_0^t (m - x_2(s)) x_2(s) ds,$$

one gets

$$\begin{aligned} U^N(t) &= \alpha \sqrt{N} \int_0^t \left(\bar{X}_1^N(s)^2 - r^2 (m - x_2(s))^2 \right) ds \\ &\quad + \beta \sqrt{N} \int_0^t \left(\bar{X}_1^N(s) \bar{X}_2^N(s) - r (m - x_2(s)) x_2(s) \right) ds + \frac{M_2^N(Nt)}{\sqrt{N}} + O(1/\sqrt{N}). \end{aligned}$$

Concerning the martingale term, Relation (11) gives, for $t \geq 0$,

$$\left\langle \frac{M_2^N}{\sqrt{N}} \right\rangle (Nt) = 2\alpha \int_0^t \bar{X}_1^N(s)^2 ds + \beta \int_0^t \bar{X}_1^N(s) \bar{X}_2^N(s) ds + O(1/N).$$

With the same method as in the proof of Theorem 1, one gets the following convergence in distribution

$$\lim_{N \rightarrow +\infty} \left(\left\langle \frac{M_2^N}{\sqrt{N}} \right\rangle (Nt) \right) = \left(2\alpha r^2 \int_0^t (m - x_2(s))^2 ds + \beta r \int_0^t x_2(s) (m - x_2(s)) ds \right)$$

by Relation (27).

Note also that, for $s \geq 0$,

$$\begin{aligned} \sqrt{N} \left(\bar{X}_1^N(s) \bar{X}_2^N(s) - r (m - x_2(s)) x_2(s) \right) \\ = U^N(s) \bar{X}_1^N(s) + \sqrt{N} \left(\bar{X}_1^N(s) - r (m - x_2(s)) \right) x_2(s) \end{aligned}$$

and

$$(28) \quad \sqrt{N} \left(\bar{X}_1^N(s) - r (m - x_2(s)) \right) = -\frac{\sqrt{N}}{\gamma + \gamma^*} \left(\gamma \bar{X}_0^N(s) - \gamma^* \bar{X}_1^N(s) \right) - r U^N(t).$$

The above relation for $(U^N(t))$ can then be rewritten as

$$\begin{aligned} (29) \quad U^N(t) &= \int_0^t U^N(s) \left((\beta - \alpha r) \bar{X}_1^N(s) - \alpha r^2 (m - x_2(s)) - \beta r x_2(s) \right) ds \\ &\quad - \frac{1}{\gamma + \gamma^*} \int_0^t (\gamma^* y - \gamma x) [\alpha (y + r(m - x_2(s))) + \beta x_2(s)] \sqrt{N} \mu_N(dx, dy, ds) \\ &\quad + \frac{M_2^N(Nt)}{\sqrt{N}} + O(1/\sqrt{N}). \end{aligned}$$

The convergence in distribution of the martingale, Proposition 4 and the criterion of the modulus of continuity give easily the tightness of the sequence $(U^N(t))$. Let $(U(t))$ be a limit of some subsequence $(U^{N_k}(t))$.

A close look at Relation (29) shows that the theorem will be proved, with standard arguments, if the following convergence in distribution is proved

$$\lim_{k \rightarrow +\infty} \left(\int_0^t U^{N_k}(s) \overline{X}_1^{N_k}(s) \, ds \right) = \left(r \int_0^t U(s)(m - x_2(s)) \, ds \right).$$

For $k \geq 0$,

$$\begin{aligned} & \int_0^t U^{N_k}(s) \overline{X}_1^{N_k}(s) - rU(s)(m - x_2(s)) \, ds \\ &= \int_0^t U^N(s) \left(\overline{X}_1^N(s) - r(m - x_2(s)) \right) \, ds + \int_0^t r(m - x_2(s)) (U^N(s) - U(s)) \, ds, \end{aligned}$$

the process associated to the last term of the second part of this identity converges in distribution to 0. By Relation (28), the first term can be written as

$$\begin{aligned} & - \int_0^t \left(\overline{X}_2^{N_k}(s) - x_2(s) \right) \left(\frac{\sqrt{N_k}}{\gamma + \gamma^*} \left(\gamma^* \overline{X}_0^{N_k}(s) - \gamma \overline{X}_1^{N_k}(s) \right) + rU^{N_k}(t) \right) \, ds \\ &= -r \int_0^t \left(\overline{X}_2^{N_k}(s) - x_2(s) \right) U^{N_k}(s) \, ds \\ & \quad - \frac{1}{\gamma + \gamma^*} \int_0^t \left(\frac{M_{N_k}}{N_k} - x - y - x_2(s) \right) (\gamma x - \gamma^* y) \sqrt{N_k} \mu_{N_k}(dx, dy, ds). \end{aligned}$$

the first term of the right hand side converges in distribution to 0 due to Theorem 1 and the same property also holds for the second term by Proposition 4. The theorem is proved. \square

As a consequence, one gets the following central limit theorem for the lag time. The notations of Corollary 1 and Theorems 1 and 2 are used.

Corollary 2. *Under the scaling regime (2), for $\delta \in (0, 1)$, the convergence in distribution*

$$(30) \quad \lim_{N \rightarrow +\infty} \frac{T^N(\delta) - Nt_\delta}{\sqrt{N}} = \frac{\delta\eta - U(t_\delta)}{rm^2(1-\delta)(\beta + \alpha r(1-\delta))}$$

holds, where the variables $T^N(\delta)$ and t_δ are defined by (23) and (24) and $(U(t))$ by (26), and $r = \gamma/(\gamma + \gamma^*)$.

Proof. For $z \in \mathbb{R}$ note that, since $(X_2^N(t))$ is a non-decreasing process,

$$\begin{aligned} \left\{ \frac{T^N(\delta) - Nt_\delta}{\sqrt{N}} \geq z \right\} &= \{ X_2^N(s_N) < \delta M_N \} \\ &= \left\{ \frac{\overline{X}_2^N(s_N) - Nx_2(s_N/N)}{\sqrt{N}} < \frac{\delta M_N - Nx_2(s_N/N)}{\sqrt{N}} \right\}, \end{aligned}$$

with $s_N = Nt_\delta + z\sqrt{N}$. From Theorem 2 one gets the convergence in distribution

$$\lim_{N \rightarrow +\infty} \frac{\overline{X}_2^N(s_N) - Nx_2(s_N/N)}{\sqrt{N}} = U(t_\delta)$$

and the expansion of $(x_2(t))$ at t_δ gives

$$\lim_{N \rightarrow +\infty} \frac{\delta M_N - N x_2(s_N/N)}{\sqrt{N}} = \delta \eta - z r m^2 (1 - \delta) (\beta + \alpha r (1 - \delta)).$$

This completes the proof of the corollary. \square

Equation (30) shows that the variance of the lag time is inversely proportional to γ/γ^* , a low misfolding rate will thus increase the variability of the polymerisation process.

3. MODELS WITH SCALED REACTION RATES

For $t \geq 0$, $X_1^N(t)$ is the number of monomers at time t and $X_2^N(t)$ is the number of polymerized monomers. The initial condition is $X_1^N(0) = M_N$ and $X_2^N(0) = 0$. Because of the relation of conservation of mass, one has $M_N = X_1^N(t) + X_2^N(t)$.

It is not difficult to see that the process $(X_2^N(t))$ can be represented as the solution of the following stochastic differential equations,

$$(31) \quad dX_2^N(t) = 2 \sum_{i=1}^{X_1^N(X_1^N-1)(s-)/2} \mathcal{N}_{\alpha/N^{\nu+2}}^i(dt) + \sum_{i=1}^{X_1^N(s-)X_2^N(s-)} \mathcal{N}_{\beta/N^2}^i(dt).$$

By integrating this equation, one gets the relation

$$(32) \quad X_2^N(t) = \frac{\alpha}{N^{2+\nu}} \int_0^t X_1^N(s)(X_1^N(s)-1) ds + \frac{\beta}{N^2} \int_0^t X_1^N(s)X_2^N(s) ds + M^N(t),$$

where $(M^N(t))$ is a martingale whose previsible increasing process is given by

$$(33) \quad \langle M \rangle_N(t) = 2 \frac{\alpha}{N^{2+\nu}} \int_0^t X_1^N(s)(X_1^N(s)-1) ds + \frac{\beta}{N^2} \int_0^t X_1^N(s)X_2^N(s) ds.$$

The following proposition shows that, on the time scale $t \mapsto Nt$, the polymerised mass is for this model in the order of $N^{1-\nu}$.

Proposition 5. *Under the scaling condition (2), for the convergence in distribution, the relation*

$$\lim_{N \rightarrow +\infty} \left(\frac{X_2^N(Nt)}{N^{1-\nu}} \right) = \left(\frac{\alpha m}{\beta} (e^{\beta m t} - 1) \right)$$

holds.

Proof. The proof is standard by using the identities (32) and (33), and the relation $X_1^N(t) + X_2^N(t) = M_N$. See Eugène et al. [10] for example. \square

The following lemma introduces a branching process which will be helpful to estimate the order of magnitude in N of the lag time

$$T^N(\delta) = \inf\{t \geq 0 : X_2^N(t)/M_N \geq \delta\},$$

for $0 < \delta < 1$.

Lemma 1. *For $a, b > 0$, let $(W_{a,b}^N(t))$ be a pure birth process with birth rate*

$$\frac{a}{N^\nu} + \frac{b}{N} x$$

in state $x \in \mathbb{N}$, with $W(0) = 0$ and $0 < \nu \leq 1$. If

$$\tau_{a,b}^N(\delta) \stackrel{def.}{=} \inf\{t > 0 : W_{a,b}^N(t) \geq \delta N\},$$

then the sequence $(\tau_{a,b}^N(\delta)/(N \log N))$ converges in distribution to ν/b .

As it can be seen $(W_{a,b}^N(t))$ is a branching process with immigration. Immigration rate is a/N^ν and the reproduction rate is given by b/N . See Harris [12] for example.

Proof. Let, for $x \in \mathbb{N}$, E_x^N denotes an exponential random variable with parameter $a/N^\nu + xb/N$, assuming that the random variables E_x^N , $x \geq 0$ are independent, then clearly

$$\tau_{a,b}^N(\delta) \stackrel{\text{dist}}{=} \sum_{x=0}^{\lfloor \delta N \rfloor} E_x^N.$$

hence after some simple estimations

$$\lim_{N \rightarrow +\infty} \frac{\mathbb{E}(\tau_{a,b}^N(\delta))}{N \log N} = \frac{\nu}{b}.$$

In the same way, one checks that the sequence $(\text{Var}(\tau_{a,b}^N(\delta)/N))$ is bounded

$$(34) \quad \text{Var} \left(\frac{\tau_{a,b}^N(\delta)}{N} \right) \leq \sum_{x=0}^{+\infty} \frac{1}{(aN^{1-\nu} + xb)^2}.$$

The convergence in distribution follows, by using Chebishev's Inequality. \square

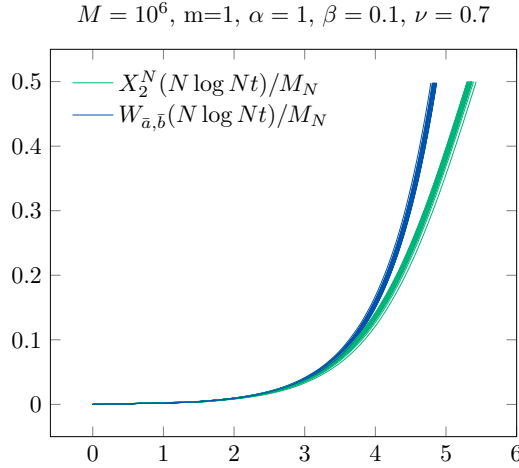


FIGURE 1. In blue, 20 simulations of $(W_{a,b}/M_N)$ and in green, 20 simulations of (X_2^N/M_N) on the time scale $t \mapsto N \log Nt$.

Let $0 < \delta < 1$ and fix some $\underline{\kappa} < 1 < \bar{\kappa}$, one can assume that N is sufficiently large so that $\underline{\kappa} \leq M_N/(mN) \leq \bar{\kappa}$ holds. Recall that $T^N(\delta)$ is the first time that the fraction of the number of polymerised monomers $X_2^N(t)/M_N$ is greater than δ . The transition rates of $(X_2^N(t))$ are given by

$$(35) \quad x \mapsto \begin{cases} x+2 & \text{at rate } \alpha/N^\nu [(M_N - x)/N]^2 \\ x+1 & \text{at rate } \beta x/N \times (M_N - x)/N. \end{cases}$$

By comparing the transition rates, we see that, for $x < \delta M_N$ one has

$$\begin{cases} \alpha/N^\nu ((M_N - x)/N)^2 \geq \alpha/N^\nu (\underline{\kappa}m)^2(1 - \delta)^2, \\ \beta x/N \times (M_N - x)/N \geq \beta \underline{\kappa}m(1 - \delta). \end{cases}$$

One can therefore construct a coupling such that, on the event $\{T^N(\delta) > t\}$, the relation $X_2^N(t) \geq W_{\underline{a}, \underline{b}}(t)$ holds with $\underline{a} = \alpha \underline{\kappa} m^2 (1 - \delta)^2$ and $\underline{b} = \beta \underline{\kappa} m (1 - \delta)$. One obtains the relation $\tau_{\underline{a}, \underline{b}}^N(\delta m) \geq_{st} T^N(\delta)$, where \geq_{st} denotes the stochastic order: if U and V are two real valued random variables

$$U \geq_{st} V \text{ if } \mathbb{P}(V \geq x) \leq \mathbb{P}(U \geq x) \quad \forall x \in \mathbb{R}.$$

Since $X_2^N(t) \leq 2W_{\bar{a}, \bar{b}}(t)$, with $\bar{a} = \alpha(\bar{\kappa}m)^2$ and $\bar{b} = \beta\bar{\kappa}m$, one has $\tau_{\bar{a}, \bar{b}}^N(\delta m/2) \leq_{st} T^N(\delta)$. One gets therefore

$$(36) \quad \tau_{\bar{a}, \bar{b}}^N(\delta m/2) \leq_{st} T^N(\delta) \leq_{st} \tau_{\underline{a}, \underline{b}}^N(\delta m).$$

Since the constants $\underline{\kappa}$ and $\bar{\kappa}$ can be chosen arbitrarily close to 1, the following proposition has therefore been proved.

Proposition 6 (Order of Magnitude of Lag Time). *For $\delta > 0$ and $0 < \nu \leq 1$,*

$$\lim_{N \rightarrow +\infty} \mathbb{P} \left(\frac{\nu}{\beta m} \leq \frac{T^N(\delta)}{N \log N} \leq \frac{\nu}{\beta m(1 - \delta)} \right) = 1.$$

Remark. It is very likely that, to reach the state δN , only the second reaction has a real impact as soon as the variable X_2^N is not 0. If true, simple calculations, as in the proof of the above lemma, would then give that the variable $T^N(\delta)/(N \log N)$ is converging in distribution to $\nu/(\beta m)$ as N get large. Note that the limit in this asymptotic result does not depend on δ which suggests a sharp transition for the polymerisation process.

The birth process $(W_{\bar{a}, \bar{b}}(t))$ seems to be close to $(X_2^N(t))$ during the initiation of the polymerisation, as the simulations of Figure 1. This suggests that, for δ small, the variables $\tau_{\bar{a}, \bar{b}}^N(\delta m)$ and $T^N(\delta)$ are very close. We conclude this part by considering the case $\nu > 1$.

A Very Slow Nucleation Step. Now we assume that $\nu > 1$, in this regime, the first reaction, the nucleation step, is then significantly slowed.

Proposition 7. *For any $\varepsilon > 0$ and $0 < \delta < 1$, there exist $0 < K_1 < K_2$ such that*

$$\liminf_{N \rightarrow +\infty} \mathbb{P} \left(K_1 \leq \frac{T^N(\delta)}{N^\nu} \leq K_2 \right) \geq 1 - \varepsilon.$$

Proof. By using Relation (36), it is enough to derive a corresponding limit theorem for $\tau_{a, b}^N(\delta)/N^\nu$ for some $a > 0$ and $b > 0$. Let (E_x^1) be a sequence of i.i.d. exponential random variables with parameter 1, then

$$(37) \quad \frac{\tau_{a, b}^N(\delta)}{N^\nu} = \sum_{x=0}^{\lfloor \delta N \rfloor} \frac{E_x^1}{a + xbN^{\nu-1}} = \frac{E_0^1}{a} + \sum_{x=1}^{\lfloor \delta N \rfloor} \frac{E_x^1}{a + xbN^{\nu-1}}.$$

The expected value of the last term of the right hand side of the above relation is bounded by $K \log(N)/N^{\nu-1}$ for some constant $K > 0$. Consequently, this term becomes negligible in distribution for N large. One gets that the variable $\tau_{a, b}^N(\delta)/N^\nu$ converges in distribution to an exponential random variable. The proposition is proved. \square

As we have seen in the proof, the only term that matters in the series in Relation (37) is the first one: the time to reach one polymerised monomer. It characterises the order of magnitude of the lag time. This variable has been analysed in Szavits-Nossan et al. [28] and Yvinec et al. [30].

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